Chiral Recognition in Cyclic α-Hydroxy Carbonyl Compounds: A Theoretical Study

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A theoretical study (DFT and MP2) of the self-association of homochiral (*RR* or *SS*) and heterochiral (*RS* or *SR*) dimers of three series of cyclic α-hydroxy-carbonyl derivatives has been carried out. The solvation effect on the parent derivative dimers has been explored, showing nonsignificant changes in the configurations preferred but altering in some cases the homo/heterochiral preference of the dimers. The results in the gas phase of the systems with different substituents show a preference for the heterochiral dimers. The energetic results have been analyzed with the NBO and AIM methodologies. Optical rotatory power calculations of the monomers and homochiral dimers show large variations of this parameter depending on the substituents and the complexation.

Introduction

The chiral nature of biological molecules provides an environment where the recognition and reactivity of a given enantiomer is discriminated versus its corresponding mirror image. In many of these processes, the role of hydrogen bonds (HB) is very important. Nature has selected a unique enantiomeric form for their two main building blocks, amino acids and sugars. The mechanisms responsible for this selection have recently been reviewed by Cintas et al.[1,2] A Diels−Alder reaction using a chiral catalyst that is involved in the transition state (TS) through HBs has recently been described.[3]

The different reactivity of pure enantiomeric mixtures and racemic ones, as proposed by Wynberg and Feringa in 1976,[4] is based on the difference of what they call the ‘‘enantiomeric recognition’’ effect in the former case and ‘‘antipodal interaction’’ in the latter. In the same year, Craig and Mellor[5] reviewed the energetic sources of the chiral discrimination in intermolecular interactions.

Several theoretical articles have addressed chiral self-recognition as in the case of a series of α-amino alcohols,[6] in complexes of compounds with axial chirality,[7] in pyrrolo[2,3-*c*]pyrrole dimers,[8] and in dimers and trimers of sulfoxide derivatives where, in addition, the corresponding proton-transfer processes have been treated.[9] The effect of fluoro substitution in the relative energy of diasteromeric derivatives of diphenylborate and isoelectronic structures has been explored.[10] The solvent effect on the chiral discrimination has been studied in dimers of hydrogen peroxide and its methyl derivative.[11] The study of the diastereomeric interaction between a chiral system and the two enantiomeric forms of another molecule has been carried out for simple ethers, oxirane derivatives, and hydrogen peroxide.[12] The interaction of 2-naphthyl-1-ethanol with chiral and nonchiral alcohols has been studied experimental and theoretically.[13,14]

The study of chiral clusters in the gas phase has been carried out using different spectroscopic techniques.[15] King and Howard reported a microwave study of the heterochiral dimer of 2-butanol.[16] Suhm et al. have examined the dimers of glycidol by means of FTIR spectroscopy.[17] Beu and Buck found evidence of the presence of different chiral isomers in the IR spectra of hydrazine clusters.[18] Zehnacker-Rentien et al. have studied the complexes of 2-naphthyl-1-ethanol with chiral systems using IR/UV double-resonance spectroscopy.[14] Speranza et al. used resonance-enhanced two-photon ionization (R2PI) spectroscopy to study the chiral complexes of alcohol dimers[19] and mass spectrometry in the case of metallic complexes of α-aminophosphonic acids.[20]

The α-hydroxy carbonyl function is present in a number of organic and bioorganic compounds as lactate derivatives, citrates, steroids, and ascorbic acid among others and can be considered to be analogues to the amino acids in their HB donor/acceptor properties. In addition, the syntheses of some of the compounds considered in the present article have been described, including the case of 2-hydroxycyclobutanone (**2**, X = H) that is reported in the *Organic Synthesis* series.[21] Furthermore, recent experimental work by Borho and Suhm has dealt with the chiral recognition in clusters of methyl lactate derivatives by means of *ragout*-jet FTIR spectroscopy.[22] The authors of this study have been able to assign two vibrational frequencies to the homo and heterochiral complexes of the dimer, trimer, and tetramer aggregates.

The present article will study the self-aggregation of a series of cyclic α-hydroxy carbonyl derivatives (Figure 1) by means of hydrogen bonding interactions. The chiral discrimination in gas phase and in models of solvated media has been considered. An analysis of the interactions dealing with the chiral discrimination has been carried out using NBO and AIM methods. Finally, the effect of aggregation of homochiral mixtures on the optical rotation of these compounds has been studied.

Methods

The geometry of the monomers and compounds has been optimized using the Gaussian 98 and Gaussian 03 packages[23,24] and the B3LYP[25] hybrid DFT-HF method with the 6-31+G** basis set.[26] The minimum nature of the structures has been confirmed by frequency calculation. Further geometry optimization has been carried out at the MP2/6-311+G** computational level.[27]

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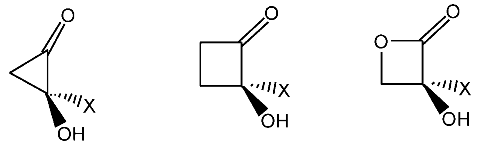


1 **2** **3**

Figure 1. Schematic representation of the compounds studied.

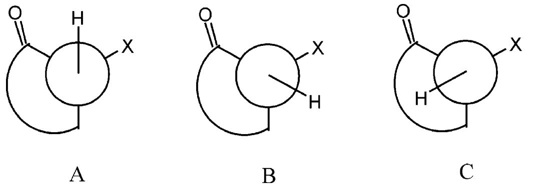


Figure 2. Conformational possibilities of the OH moiety viewed along the O−C bond.

The interaction energy has been corrected for the inherent basis set superposition error (BSSE) using the full counterpoise method as proposed by Boys and Bernardi.[28]

The solvation effect has been evaluated using the continuum model developed by Tomasi's group, known as PCM,[29] for the H_2O, CH_3OH, and CCl_4 solvents, which represents a wide range of dielectric constants. This model does not consider specific interactions and thus in some cases does not properly represent the solvent−solute interaction. In those cases, it is necessary to use explicit solvent molecules in conjunction with the PCM model.

The natural bond orbital (NBO) method[30] has been used to characterize the orbital interactions between filled (donor) and empty (acceptor) orbitals within the dimers. The formation of a hydrogen bond (HB) is associated with an interaction of the lone pair of the electron donor atom and the σ antibonding orbital of the HX moiety that acts as an electron acceptor.

The electron density has been characterized using the atoms in molecules (AIM) methodology.[31] In all cases where a hydrogen bond interaction is formed, the corresponding bond critical point (bcp) is found. In addition, other intermolecular interactions present bcp that allow us to explain the relative stability of the dimers studied.

The optical rotatory power has been calculated in the monomers and homochiral dimers at the B3LYP/6-311++G(2d,2p) computational level as recommended in the literature.[32,33] using the optimized MP2/6-311+G** geometries.

Results and Discussion

Three systems have been considered in the present study (Figure 1). Even though the presence of a ring limits the flexibility of the systems, an adequate disposition of the OH moiety should be present to obtain dimers of these compounds. Thus, the three possible dispositions of this group have been explored as indicated in the Newman projections in Figure 2. For the parent compounds (X = H), the lowest-energy minima correspond to conformation A at the B3LYP/6-31+G** computational level, with the relative energy of conformation B of **1** being 0.90 kcal/mol and that of conformation C of **2** being 0.69 kcal/mol. The rest of the conformations collapse to conformation A in the optimization process. It is noteworthy that conformation A is the most adequate one to form dimers where each monomer acts simultaneously as a HB donor and acceptor with different atoms.

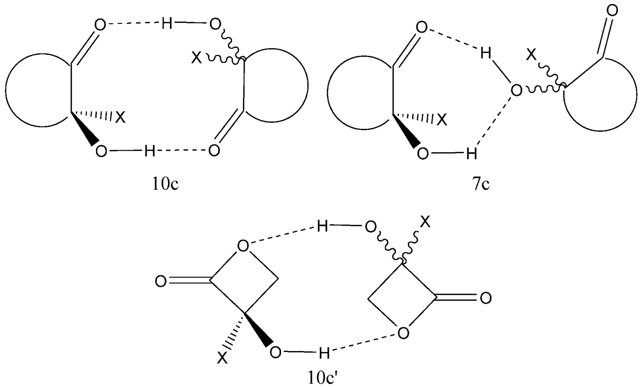


Figure 3. Schematic representation of the dimer structures considered.

TABLE 1: Relative Energy of the Complexes Shown in Figure 3 Calculated at the B3LYP/6-31+G Level**

compound	chirality	disposition	E_{rel} (kcal/mol)
1 (X = H)	*R*/*R*	**10c**	0.65
1 (X = H)	*R*/*S*	**10c**	**0.00**
1 (X = H)	*R*/*R*	**7c**	3.42
1 (X = H)	*R*/*S*	**7c**	3.64
2 (X = H)	*R*/*R*	**10c**	0.16
2 (X = H)	*R*/*S*	**10c**	**0.00**
2 (X = H)	*R*/*R*	**7c**	1.26
2 (X = H)	*R*/*S*	**7c**	3.15
3 (X = H)	*R*/*R*	**10c**	0.69
3 (X = H)	*R*/*S*	**10c**	**0.00**
3 (X = H)	*R*/*R*	**7c**	3.32
3 (X = H)	*R*/*S*	**7c**	5.18
3 (X = H)	*R*/*R*	**10c′**	11.70
3 (X = H)	*R*/*S*	**10c′**	6.53

Several potential dimers have been initially considered in the parent compound derivatives as indicated in Figure 3. The dispositions have been named on the basis of the number of bonds in the cycle formed by the HBs. The first two dispositions (**7c** and **10c**) are common for the three compounds considered here, whereas the last one (**10c′**) is unique for **3**. The relative energies obtained for the homo and heterochiral dispositions are gathered in Table 1. In all cases, the most stable configurations correspond to those of **10c** for the heterochiral complexes followed by the homochiral one. The E_{rel} of the **7c** complexes is above 3 kcal/mol with the exception of that of the homochiral complex of **2**, whose E_{rel} is 1.3 kcal/mol. The two complexes of the **10c′** configuration present very large E_{rel} values (11.7 and 6.5 kcal/mol for the homo and heterochiral complexes, respectively). The present results are in agreement with those described by Suhm for methyl lactate dimers where the **10c** configurations are found to be more stable than the **7c** ones by about 1.2 kcal/mol at B3LYP/6-31+G* level and about 2.4 kcal/mol at the MP2/6-31+G* level.[22]

It should be noted that the present results correspond to a gas-phase environment that is not the usual one in biology and organic chemistry, although in the ligand−protein (drug-receptor) interactions it is usually assumed that there are no solvent molecules. In addition, the importance of the solvent in the chiral recognition tendencies and in the preferred configuration in those processes has been shown previously.[6,11] Thus, the effect of the solvation process on several solvents has been evaluated for configurations **10c** and **7c**. The relative energies with the solvation energies are reported in Table 2.

In all cases, the E_{rel} of the homochiral complex in configuration **10c** became smaller as the solvent became more polar, and in one case (**2**), it is more stable than the heterochiral complex considering the effect of water and methanol as solvents.

In the same way, the E_{rel} values of the **7c** configurations are smaller than in the gas phase with the exception of the

TABLE 2: Relative Energy of the Configurations Shown in Figure 3 Including the Solvent Effect (PCM) Calculated at the B3LYP/6-31+G Level**

compound	chirality	disposition	E_{rel} (kcal/mol) H_2O	E_{rel} (kcal/mol) CH_3OH	E_{rel} (kcal/mol) CCl_4
1 (X = H)	*R*/*R*	**10c**	0.30	0.33	0.62
1 (X = H)	*R*/*S*	**10c**	**0.00**	**0.00**	**0.00**
1 (X = H)	*R*/*R*	**7c**	2.21	2.45	3.05
1 (X = H)	*R*/*S*	**7c**	2.34	2.59	3.28
2 (X = H)	*R*/*R*	**10c**	**0.00**	**0.00**	0.17
2 (X = H)	*R*/*S*	**10c**	0.26	0.19	**0.00**
2 (X = H)	*R*/*R*	**7c**	2.11	2.17	1.48
2 (X = H)	*R*/*S*	**7c**	2.14	2.23	2.79
3 (X = H)	*R*/*R*	**10c**	0.38	0.45	0.75
3 (X = H)	*R*/*S*	**10c**	**0.00**	**0.00**	**0.00**
3 (X = H)	*R*/*R*	**7c**	3.12	3.28	3.36
3 (X = H)	*R*/*S*	**7c**	2.91	3.13	4.49

TABLE 3: Geometrical Characteristics of the HB Formed[a] Calculated at the B3LYP/6-31+G and MP2/6-311+G** Levels[b,c]**

		1		**2**		**3**	
X	chirality	O···H	OHO	O···H	OHO	O···H	OHO
H	*R*/*R*	1.862	175.9	1.868	173.6	1.857	169.8
		(1.884)	(173.9)	(1.934)	(160.1)	(1.903)	(160.5)
H	*R*/*S*	1.850	175.0	1.846	170.3	1.820	174.1
		(1.873)	(174.2)	(1.875)	(162.6)	(1.841)	(172.7)
F	*R*/*R*	1.826	172.9	1.822	172.4	1.784	179.0
		(1.854)	(171.7)	(1.849)	(174.1)	(1.816)	(176.5)
F	*R*/*S*	1.823	173.0	1.822	173.6	1.778	179.5
		(1.849)	(171.5)	(1.851)	(171.2)	(1.815)	(175.7)
Cl	*R*/*R*	1.843	171.4	1.812	170.3	1.789	173.0
		(1.850)	(172.8)	(1.829)	(172.3)	(1.813)	(176.5)
Cl	*R*/*S*	1.832	173.5	1.802	171.3	1.778	179.2
		(1.840)	(171.0)	(1.824)	(170.9)	(1.795)	(175.7)
Br	*R*/*R*	1.801	172.8	1.761	173.3	1.758	179.9
Br	*R*/*S*	1.791	171.1	1.751	172.5	1.735	178.8
CH_3	*R*/*R*	1.876	174.7	1.902	177.5	1.887	173.7
		(1.894)	(170.8)	(1.921)	(176.0)	(1.892)	(174.1)
CH_3	*R*/*S*	1.863	173.7	1.874	172.7	1.844	179.7
		(1.871)	(172.4)	(1.879)	(166.0)	(1.850)	(177.2)
CF_3	*R*/*R*	1.862	172.7	1.873	167.8	1.843	170.0
CF_3	*R*/*S*	1.854	175.8	1.858	170.0	1.821	176.6
$C(CH_3)_3$	*R*/*R*	1.891	171.2	1.953	162.3	1.902	167.8
$C(CH_3)_3$	*R*/*S*	1.871	178.6	1.926	166.5	1.883	170.9

[a] Å and deg. [b] In parentheses. [c] Because of the symmetry of the dimers, only one HB is reported.

homochiral complex of **2** where E_{rel} increases. In any case, the relative energy with the inclusion of the solvent effect only in one case is below 2.0 kcal/mol.

Because in all of the environments considered here the **10c** configurations are more stable than the **7c** ones, only the former ones will be considered in the derivatives of **1**−**3**.

Some of the geometrical characteristics of the complexes studied are gathered in Table 3. The HB distance ranges from 1.95 to 1.74 Å in each series, with the shortest one being the heterochiral Br complex and the longest one being the homochiral of the *tert*-butyl derivative. The B3LYP/6-31+G** geometries are systematically shorter than the MP2/6-311+G** ones, 0.023 Å on average. Regarding the differences between the homo and heterochiral complexes, the latter shows in all cases shorter H···O distances with the exception of the fluoro derivatives of **2**.

The OHO HB angle that provides a measure of the linearity of the systems shows values larger than 170° with a few exceptions, in general related to the more bulky substituents [CF_3 and $C(CH_3)_3$].

The calculated interaction energies for the derivatives of **1**−**3** are summarized in Table 4. In general, the B3LYP/6-31+G** results are more negative than the MP2/6-311+G** ones by 1.4 kcal/mol on average with a maximum value of 2.2 kcal/mol. The results of Table 4 show that the interaction energies range from −7.0 to −13.9 kcal/mol. Considering that two HBs are formed in the present complexes, the strength of each one is similar to that found experimentally in the water dimer (−5.4 ± 0.7 kcal/mol).[34] The larger interaction energies are obtained for **3**, followed by the complexes of **1**, with those of **2** being the less stable ones for a given substituent and chiral disposition. Regarding the substituents, the more bulky ones, CF_3 and $C(CH_3)_3$, show smaller interaction energies, whereas the heterochiral dimer of the parent compounds is the one with the larger interaction energy in two of the three series (**2** and **3**). Thus, acceptable correlation coefficients (between 0.83 and 0.95) are obtained for the interaction energy versus the Taft *Es* steric parameter[35] for the homo and heterochiral complexes in each of the series of compounds studied.

The chiral selectivities, calculated as the difference between the homo and heterochiral dimers, are gathered in Table 5. The B3LYP/6-31+G** results favor the heterochiral complex except in three cases where the homochiral complex is slightly more stable. At the MP2/6-311+G** level, the preferences are divided approximately half and half, but in those cases where the chiral discrimination is above 0.5 kcal/mol, as for the methyl derivatives and the parent dimers of **1** and **3**, both methods show the same tendency. It has been mentioned that the failure of the DFT methods to evaluate the dispersion forces[12] of the substituents in the homochiral complexes could be responsible for the differences found. These results and the experimental evidence of the lack of chiral selectivity in the methyl lactates[22] indicate the dependence of this property on the molecular systems and the substituents present.

Considering that the methyl group is not the largest of the substituents considered here and is not the one with an important concentration of charge, as is CF_3, it is significant that it presents some of the largest chiral discrimination in each series of compounds. Similar results have been reported in other compounds, indicating the special characteristic of this substituent in the chiral recognition processes.[8]

To understand the energetic characteristics of these complexes, the stabilization energy due to the interaction of the lone pair of the oxygen and the antibonding O−H orbital that form the HB have been evaluated with the NBO method (Table 6). In addition, the energy destabilization in the monomers, due to the formation of the dimer, has been calculated (Table 6). The orbital stabilization due to the formation of the HB ranges from 8 to 24 kcal/mol. The good linear relationship found between this parameter and the HB distance (Figure 4) is significant, in agreement with the general belief that shorter HBs are indicative of stronger interactions. In addition, in all cases, the heterochiral complexes show stronger orbital interactions than the homochiral ones. In contrast, the monomer distortion within the dimers indicates that the homochiral dimers are favored over the heterochiral ones except for the parent dimers of **3**. The sum of the relative energies of these two parameters (homochiral minus heterochiral) correlates with the chiral discrimination in a linear fashion with acceptable correlation coefficients for each series of compounds (0.85, 0.94, and 0.84 for the complexes of **1**, **2**, and **3**, respectively).

Other possible interactions have been explored with the AIM methodology. In all cases, the corresponding bond critical points (bcp) due to the formation of the HBs have been found as well as a ring critical point in the middle of the two symmetrical HBs. More interesting, additional intermolecular bcp have been

TABLE 4: BSSE-Corrected Interaction Energies[a] of the Dimers Calculated at the B3LYP/6-31+G and MP2/6-311+G** Computational Levels**

		1		2		3	
X	chirality	B3LYP/ 6-31+G**	MP2/ 6-311+G**	B3LYP	MP2	B3LYP	MP2
H	*R*/*R*	−11.30	−9.81	−11.08	−9.79	−13.20	−11.60
H	*R*/*S*	−11.95	−10.13	−11.28	−9.08	−13.87	−11.79
F	*R*/*R*	−11.96	−10.38	−10.81	−9.22	−13.38	−11.62
F	*R*/*S*	−12.06	−10.36	−10.92	−9.08	−13.38	−11.63
Cl	*R*/*R*	−11.30	−10.39	−10.79	−9.48	−12.87	−11.75
Cl	*R*/*S*	−11.62	−10.33	−11.20	−9.33	−13.23	−11.62
Br	*R*/*R*	−10.91		−10.89		−12.75	
Br	*R*/*S*	−11.29		−11.20		−13.49	
CH_3	*R*/*R*	−10.99	−10.49	−9.76	−9.76	−11.88	−11.57
CH_3	*R*/*S*	−12.04	−10.89	−10.69	−9.89	−13.03	−12.18
CF_3	*R*/*R*	−10.29		−8.78		−10.89	
CF_3	*R*/*S*	−10.31		−9.11		−11.20	
$C(CH_3)_3$	*R*/*R*	−9.46		−7.00		−9.18	
$C(CH_3)_3$	*R*/*S*	−10.80		−8.01		−10.27	

[a] kcal/mol.

TABLE 5: Chiral Discrimination[a,b]

	1		2		3	
X	B3LYP	MP2	B3LYP	MP2	B3LYP	MP2
H	−0.65	−0.55	−0.16	0.41	−0.69	−0.25
F	−0.07	0.05	−0.08	0.19	0.01	0.19
Cl	−0.28	0.04	−0.35	0.47	−0.33	−0.13
Br	−0.40		0.01		−0.44	
CH_3	−1.05	−0.62	−0.97	−1.12	−1.15	−1.16
CF_3	0.10		−0.30		−0.25	
$C(CH_3)_3$	−1.32		−1.09		−1.09	

[a] kcal/mol. [b] The homochiral dimer is used as a reference.

TABLE 6: Orbital Stabilization Energy Due to the Formation of the HB [O(lone pair) → OH (σ*)] and Energy of Distortion for Each Monomer within the Dimer[a] Calculated at the B3LYP/6-31+G Level**

		orbital stabilization energy			monomer distortion		
X	chirality	1	2	3	1	2	3
H	*R*/*R*	15.34	15.04	14.64	0.34	0.83	1.52
H	*R*/*S*	16.22	15.48	17.65	0.46	0.94	1.18
F	*R*/*R*	17.70	17.35	20.05	0.41	0.44	0.58
F	*R*/*S*	17.83	17.48	20.53	0.41	0.48	0.64
Cl	*R*/*R*	16.46	17.95	19.42	0.38	0.53	0.58
Cl	*R*/*S*	17.29	18.74	20.62	0.39	0.58	0.64
Br	*R*/*R*	19.06	21.84	21.28	0.52	0.79	0.65
Br	*R*/*S*	20.02	22.36	24.34	0.70	1.02	0.93
CH_3	*R*/*R*	14.39	12.60	11.51	0.30	0.53	0.41
CH_3	*R*/*S*	15.61	14.75	16.72	0.42	0.69	0.53
CF_3	*R*/*R*	15.04	13.77	14.76	0.31	0.36	0.43
CF_3	*R*/*S*	15.58	15.09	17.16	0.33	0.42	0.52
$C(CH_3)_3$	*R*/*R*	12.18	7.99	10.20	0.37	0.29	0.37
$C(CH_3)_3$	*R*/*S*	14.74	11.51	13.08	0.39	0.46	0.51

[a] kcal/mol.

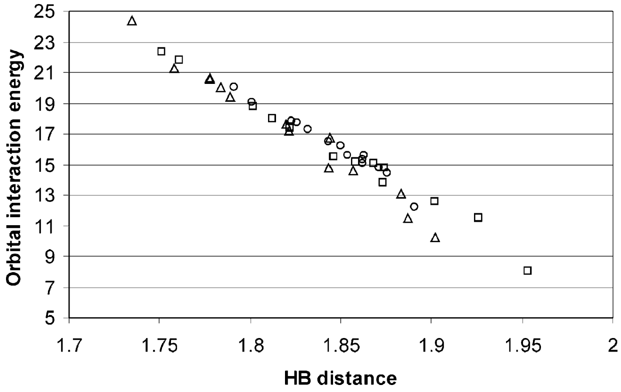


Figure 4. Orbital interaction [O(lone pair) → OH (σ*)] (kcal/mol) vs the HB distance (Å). Complexes of **1**, **2**, and **3** are represented by triangles, squares, and circles, respectively. The following linear equation can be fitted to all of the points: $E_{ORB} = 144.09 - 69.4*(\text{HB distance})$, $R^2 = 0.96$, $n = 42$.

TABLE 7: Optical Rotatory Power[a] of the Isolated Minima and Homochiral Complexes[b]

	1		2		3	
X	monomer	homochiral dimer	monomer	homochiral dimer	monomer	homochiral dimer
H	6.3	−85.8	−234.0	61.7	−178.9	−34.7
F	229.5	54.4	29.2	75.4	−0.2	−90.2
Cl	−408.0	−408.2	−262.8	−129.0	−93.3	−58.7
CH_3	−179.8	−233.2	−210.1	−157.2	−116.5	−97.6

[a] deg. [b] The configuration in all cases corresponds to that of Figure 1.

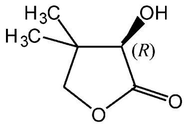
found between the substituents in all the homochiral complexes, except for X = H and F, and in some of the heterochiral ones [X = $C(CH_3)_3$ for **1**, **2**, and **3**, X = CH_3 for **2** and X = CF_3 for **3**]. The values of the electron density (small) and Laplacian (positive and small) correspond to weak closed-shell interactions. The presence of a bond critical point has been shown to correspond to a stabilization of the two atoms attached[36] and thus in some cases have been used to explain the stability of shown geometrical dispositions.[7,37] However, this local gain of energy can be compensated by the destabilization of other regions in the molecule.[6] These interactions complement the energetic results obtained for the HB interaction and the monomer distortion previously described.

The calculated optical rotatory power of the isolated monomers and the corresponding homochiral dimers is shown in Table 7. For simplicity, the configuration shown in Figure 1 has been used for all monomers and dimers. (Depending on the Cahn−Ingold−Prelog priority of the substituents, it can be *R* or *S*.) A very strong dependence on the substitution and complexation is observed in these compounds. A recent experimental and theoretical study on the aggregation effect of the pantolactone (Scheme 1) on the optical rotatory power shows important differences between the monomer (−1°) and the homochiral dimers (−200°).[38]

Conclusions

The chiral discrimination in the complexation of three series of cyclic α-hydroxyketones has been explored using DFT and

SCHEME 1: Structure of *R*-Pantolactone



Pantolactone

MP2 ab initio methods. Initially, the preferred configuration of the dimers in the gas phase and in solvent models (H_2O, CH_3OH, and CCl_4) has been established to be, in all cases, that in which each molecule acts as a HB donor and acceptor with different moieties forming a 10-membered ring.

The chiral discrimination results, at the B3LYP/6-31+G** level, favored the heterochiral complexes, whereas the tendency is not as clear at the MP2/6-311+G** level. Those cases with the larger energetic differences present similar results at the two computational levels used. As a substituent, the methyl group provides one of the largest chiral discriminations in the three series studied.

The orbital interaction between the monomers and the distortion energy is able to explain the results obtained for the chiral discrimination.

The optical rotatory power of the monomers and homochiral dimers shows a large variability depending of the substituents and the complexation, which makes its use difficult as a diagnostic tool.

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